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A model of the leech segmental swim central pattern generator

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Abstract

We present a model of the single-ganglion oscillator of the leech swim central pattern generator (CPG). The model is based on the known neuronal architecture of this circuit. Free parameters in the model were fitted to produce membrane potential oscillations matching those seen during swimming. However, the oscillations produced are not robust to small ($\pm 5\%$) changes in the parameters. We propose that this may be due to the large difference between the passive time constant of our model cells and the period of the swim oscillation. We discuss possible ways the real circuit achieves robustness.

Keywords: Leech swimming; Computational modeling; Central pattern generators

1. Introduction

How organisms produce coordinated, rhythmic behaviors such as chewing, respiration, walking, crawling, and swimming is a fundamental question in the study of

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motor control. Many of these behaviors are driven by central pattern generators (CPGs) which can produce a reasonable facsimile of the motor pattern in the absence of sensory feedback. Swimming in the leech, *Hirudo medicinalis*, is driven by a CPG, and the focus of this work is understanding how this CPG generates an oscillation. In particular, we present a model of the *segmental* swim CPG, a component of the swim CPG as a whole. Our model is, by design, very simplified. In our view, the possibility that the leech swim CPG oscillation is purely a network phenomenon has not been adequately explored in the literature. Thus we sought to examine the behaviors possible when each CPG cell is modeled as a single passive compartment, with no voltage-gated currents of any kind. In the current model, we entirely neglect cellular properties such as post-inhibitory rebound (PIR), which have been found in some of the CPG cells, and which have been proposed as possible contributors to the generation of swim oscillations. We have done this in an effort to explore whether the available data on the leech swim CPG is compatible with a purely network-mediated oscillation, with little or no contribution from these nonpassive properties.

2. Background

Swimming in the leech is governed by a CPG [10]. The neurons that form this CPG are distributed among the 21 mid-body ganglia that comprise most of the central nervous system of the animal. The swim CPG is composed of a set of eight cell pairs and one unpaired cell per ganglion, and these cells are found in nearly all of the midbody ganglia. The identified swim CPG cells and their intraganglionic synapses are shown in Fig. 1. (Similar diagrams in other published work show ten CPG cell pairs instead of eight, but we have neglected two of these cells, cells 2 and 119, both here and in the model, because of their relatively weak effects on other CPG cells [4].) During a swim episode (fictive or real), the membrane potentials of CPG cells oscillate, and drive motor neurons that produce bursts of impulses which in turn drive the muscles. One such motor neuron is cell 3, an exciter of the dorsal musculature. A simultaneous recording of the membrane potential of a CPG cell and the corresponding cell 3 action potential bursts is shown in Fig. 2. Each CPG cell's membrane potential oscillation is phase locked with the cell 3 bursts and thus with the oscillation of all the other CPG cells.

The swim CPG is 'turned on' and 'turned off' by a set of *gating cells* which are also segmentally repeated. These cells make excitatory synapses onto the swim CPG cells, and depolarization of the gating cells causes the swim CPG to 'turn on', i.e. generate an oscillation. The depolarizing current provided by the gating cells is, however, tonic rather than phasic, and so does not contribute directly to the generation of oscillations [16].

It has been shown experimentally that the CPG cells in an individual ganglion are capable of generating an oscillation in the absence of any input from the CPG cells in other ganglia [16]. The single-ganglion oscillation is not identical to that of a ganglion which still receives input from the CPG cells of neighboring ganglia, in that the individual cell waveforms and phase relationships are altered somewhat. Nonetheless,

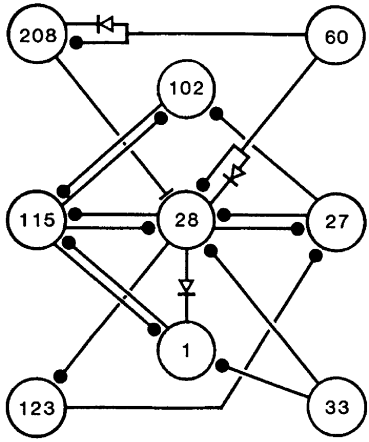

Fig. 1. Diagram of the swim CPG cells and their intraganglionic connections, modified from [1]. Bar endings represent excitatory chemical synapses, circle endings represent inhibitory chemical synapses, and diode symbols represent rectifying electrical connections.

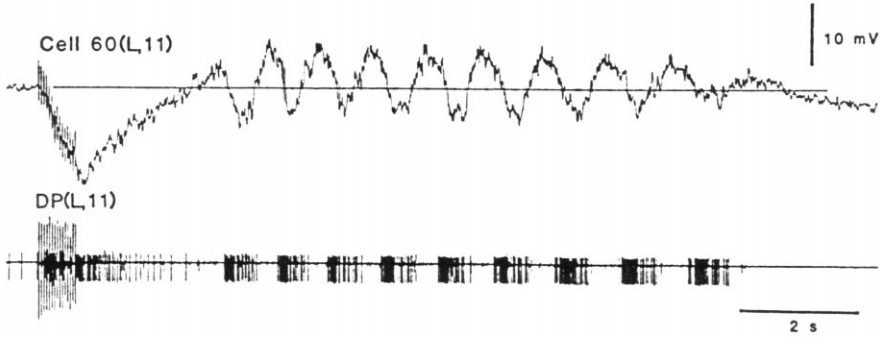

Fig. 2. Example of a simultaneous intracellular recording of a CPG cell (the cell 60 on the left side of ganglion 11) membrane potential oscillation and an extracellular recording of the cell 3 motor neuron. Figure modified from [2]. The trace labelled 'DP' is an extracellular recording of the DP (dorsal posterior) nerve, which contains a cell 3 neurite. The periodic bursts observed in this nerve during swimming are known to originate from cell 3 [12]. The horizontal line overlaid on the cell 60 trace is to indicate the rest potential of the cell.

this experiment demonstrates that an isolated ganglion contains a competent CPG. In an intact chain of ganglia, the swimming behavior arises from the segmental CPG oscillations, coordinated and modified by the interganglionic synaptic connections.

The swim CPG circuit has a number of interesting properties that are relevant to any attempt to model it. The first is that none of the swim interneurons appear to be endogenous oscillators [6]. This rules out one possible explanation of the circuit's behavior, that it is simply a collection of one or more endogenous oscillators, with the synaptic connections serving only to coordinate the individual cellular oscillators. The

second is that synaptic transmission among neurons within a segment seems to be, to a large extent, graded rather than spike-mediated [8,9]. This suggests that it may be possible to understand the circuit's behavior without including spike generation in one's model. The third is the near-absence of excitatory synapses. With the exception of cell 208, none of the CPG cells make excitatory synapses onto other CPG cells. This fact must be reflected in a model of the circuit.

An early model of this system included only the first four swim CPG cell pairs to be discovered, and was based on the hypothesis that the whole-cord CPG is composed of a number of elemental CPGs, each of which spanned two ganglia, with the overlapping of elemental CPGs providing for whole-body coordination of the swim [7]. This model is not consistent with the later discovery that a single ganglion can generate an oscillation. Later models have taken the single-segment oscillator as a given, and dealt only with modeling the intersegmental coordination as a system of coupled oscillators [13]. While these models are capable of predicting many features of intersegmental coordination, by design they are agnostic about the mechanisms generating the oscillation within a segment. Our goal here is to understand these intrasegmental mechanisms.

3. Model desiderata

The aim of this work is to develop a model of the segmental swim CPG that is consistent with the known cellular and synaptic properties of the biological system, and which produces similar behavior. By 'similar behavior', we mean:

(1) The membrane potential waveforms of the model are approximately the same as those observed in the CPG cells during swimming, and have the correct phases relative to one another.
(2) The model's frequency of oscillation increases as the tonic excitation of the system (provided by the gating cells) increases.
(3) The model is capable of oscillation in the same range of frequencies as the real system (0.5–2.0 Hz).

4. Form of the model

Our model includes the nine cell pairs and one unpaired cell which comprise the segmental swim CPG. Each cell pair is modeled as a single electrical compartment, since each cell in a pair is linked to its partner by a nonrectifying electrical connection, and the two cells exhibit very nearly identical voltage trajectories in the swimming preparation. Synapses are modeled simply as voltage-dependent ideal current sources. This is a simplification based on the idea that the changes in the driving force on the ions mediating the synaptic current due to varying postsynaptic voltage can be neglected, and the driving force assumed to be constant. In the model, the amount of current injected to the postsynaptic cell varies as a logistic function of presynaptic

voltage, up to some maximum current. This maximum current is the 'strength' of the synapse. Electrical synapses are neglected. Thus the system of equations governing our system is

$$c_m \dot{v}_i(t) = -g_l(v_i(t) - e_l) + \sum_j I_{ij}^{\text{syn}} \,\text{logistic}[4(v_j(t) - \varphi_j)/v_\beta] + x(t)\, I_i^{\text{tonic}} \quad (1)$$

where $v_i(t)$ is the membrane potential of the ith cell, c_m, g_l, and e_l are each cell's membrane capacitance, leak conductance, and leak reversal potential, respectively, I_{ij}^{syn} is the maximal synaptic current associated with the cell j's synapse onto cell i, φ_j is the synaptic half-activation voltage for cell j's synapses onto other cells, I_i^{tonic} is the level of tonic excitation cell i receives during a swim, and v_β is a variable which controls the synaptic 'gain', i.e. how steeply the sigmoid rises in its linear regime. $x(t)$ is a unitless measure of the extent to which the system is receiving excitation from the gating cells (which are themselves not included in the model), and functions as the input to the system. $x(t) = 0$ corresponds to the non-swimming state, when the gating cells are not exciting the CPG at all. $x(t) = 1$ corresponds to the state wherein the CPG is oscillating at 1 Hz, with lower/higher $x(t)$ corresponding to lower/higher frequency of oscillation.

5. Fitting to data

Since extensive data are not available on the membrane potential trajectories of CPG cells during isolated-ganglion fictive swims, we fit our model to data obtained during whole-cord fictive swimming. Those data were culled from a number of sources in the literature [2–4,6,15]. Typically, the data consisted of an intracellular recording of a single CPG cell along with a simultaneous extracellular recording of the cell 3 bursts, as shown in Fig. 2. Since the cell 3 bursts have characteristic phase relationships with the CPG cell membrane potential oscillations, it was possible to line up the CPG cell recordings in a way that approximates what one would see if one were to record from all the CPG cells in a ganglion simultaneously, a technically difficult task. These traces were normalized to have a period of 1 Hz, a frequency roughly in the middle of the range of possible swim frequencies. The traces were also low pass filtered (3 Hz cutoff) to eliminate spikes and high-frequency noise from the traces.

A model such as ours, with several unknown free parameters, is often fit to a number of input–output pairs, or targets. In our model, the input is the scalar signal $x(t)$, and the output is the vector signal $\boldsymbol{v}(t)$ (the vector of $v_i(t)$s). We used four targets in our fits. In all four targets, the input is simply a constant. The targets were as follows:

- Target 0 has $x(t) = 0$ and $v_i(t) = 0$. It represents the non-swimming, or quiescent, state of the CPG.
- Target 1 has $x(t) = 1$. $v_i(t)$ is the 1 Hz oscillation based on the data culled from the literature. This represents the basic swimming behavior.

- Target 2 has $x(t) = 0.9$. $v_i(t)$ is a time-scaled version of the oscillation data, such that the frequency of the oscillation is 0.9 Hz. This represents a slower swim than that of target 1.
- Target 3 has $x(t) = 1.1$. $v_i(t)$ is again a time-scaled version of the oscillation data, with a frequency of 1.1 Hz. This represents a faster swim than that of target 1.

The precise linear correspondence between the input magnitude and the oscillation frequency in targets 2 and 3 is simply a matter of convenience. The duration of all targets was 1.5 s, approximately one and a half cycles.

We fit our model to the data using a quasi-Newton optimization algorithm, as implemented in the Netlab software package [11] in which the time-dependent recurrent backpropagation (TDRBP) algorithm [14] is used to calculate the error gradients. From Eq. (1), the fitted parameters are the I_{ij}^{syn}s (the synaptic strengths), the φ_js (the half-activation voltage), and the I_i^{tonic}s (the amount of excitatory gating current that is injected into the cell during a 1 Hz swim). The parameters c_{m}, g_{l}, e_{l}, and v_β we hold fixed at physiologically reasonable values. In the course of fitting, the I_{ij}^{syn}s were constrained in the following way to be roughly consistent with the biology:

(1) The model cell 208 was only allowed to make excitatory synapses, and only onto two model cells, 28 and 115.
(2) Auto-synapses were not permitted.
(3) All other possible synapses were permitted, but they were constrained to be inhibitory.

These constraints are meant to reflect the general pattern of connections in the circuit, rather than the detailed pattern of connectivity.

6. Results

We performed approximately 20,000 runs of the quasi-Newton code from independent random starting points, constrained to be within reasonable physiological ranges. Of these, the majority produced models which were locally optimal, but which only fit the target data 'in the mean'. That is, the model simply settled to a steady-state for each input, with the steady-state voltage for each cell approximately equal to the time average of the corresponding target voltage. However, a small number of the runs (approximately 20) produced models capable of oscillation. These models, in addition to fitting the data over the 1.5 s period on which they were trained, appear to contain a limit cycle attractor, as one would hope. Fig. 3 shows the output of one such system compared to the 1 Hz target oscillation, for a period of 3 s. The output of the other oscillatory models was qualitatively similar, although the parameters in each case were not.

In addition to fitting the data they were designed to fit well, the oscillatory systems show some degree of generalization, in that they exhibit properties of the biological system they were not explicitly designed to have. In a sense, the fact that they oscillate, i.e. that their dynamics includes limit cycle attractors, is a generalization. This is

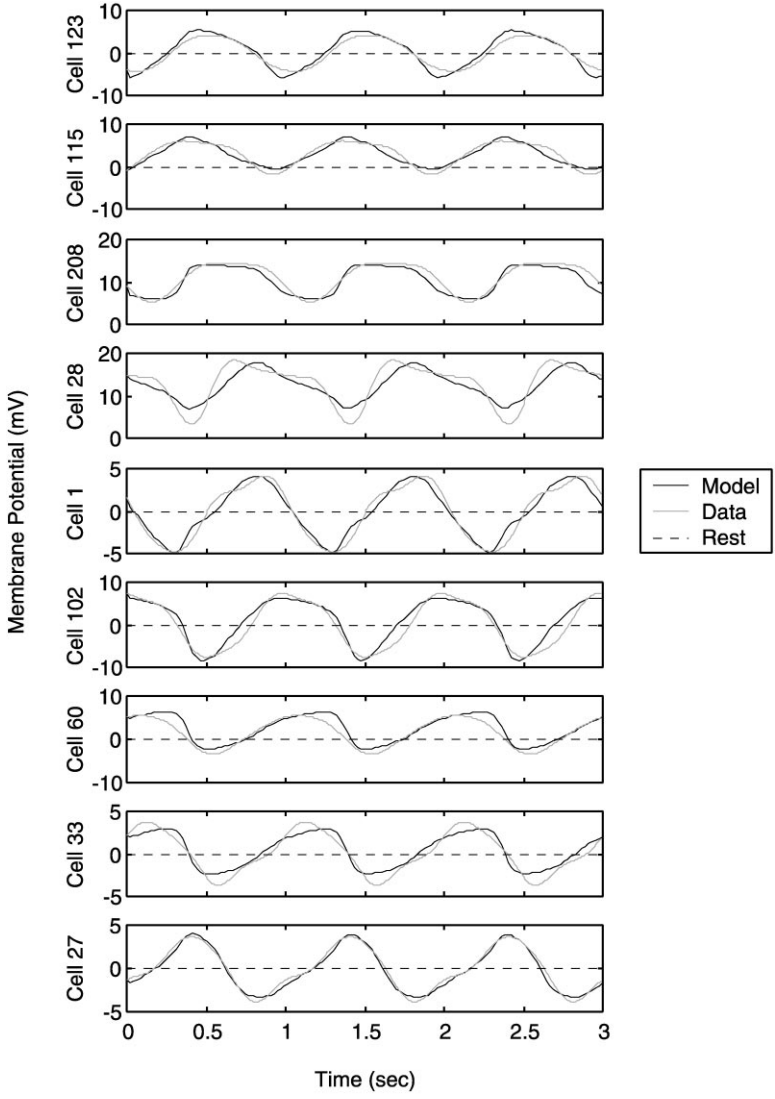

Fig. 3. Behavior of the model compared to data taken from whole-cord swims. Solid line is the model, gray line is the data, and dashed line is the resting membrane potential of the model cell. Note that the vertical axis gives millivolts relative to the resting-membrane potential.

because the fitting algorithm simply found parameters which gave good agreement with the 1.5 s targets, rather than explicitly 'designing in' a limit cycle attractor. Furthermore, the oscillatory systems were found to oscillate for values of $x(t)$ other than those of the targets, as shown in Fig. 4. In addition to interpolating reasonable oscillations for values of $x(t)$ in between those of the targets, the model also extrapolates to values of $x(t)$ outside the range of the targets.

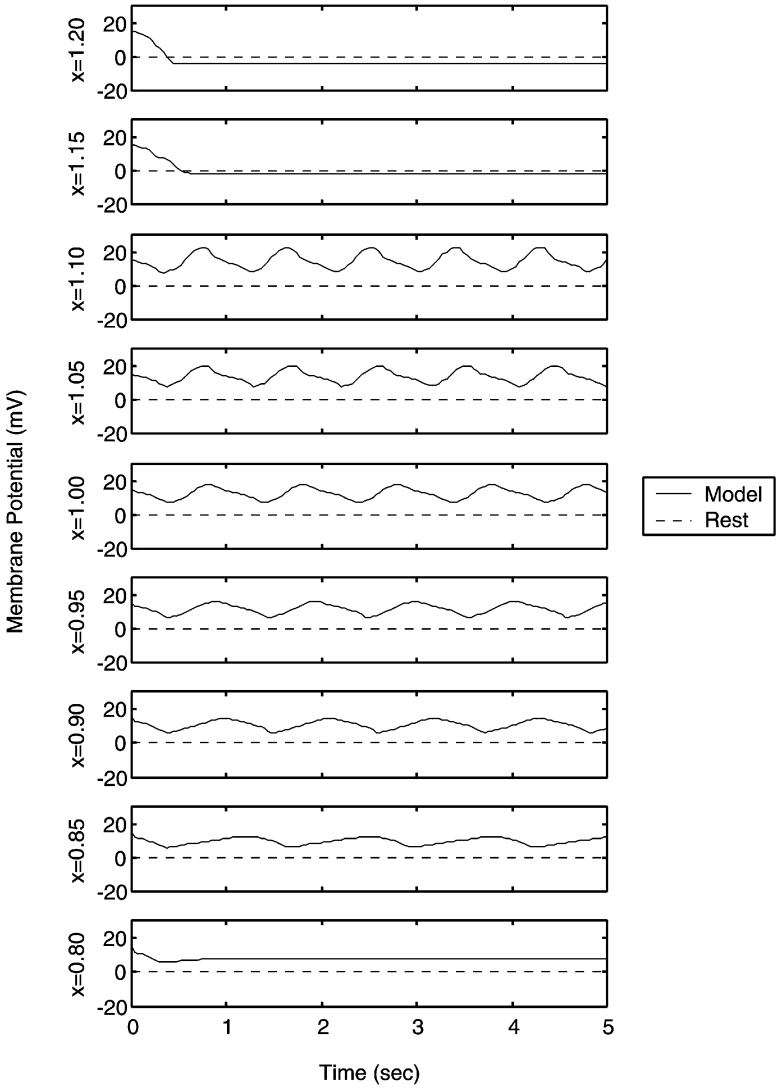

Fig. 4. Behavior of the model for varying levels of tonic excitation, $x(t)$. Graphs show the voltage trajectory of model cell 28 for different levels of $x(t)$ given at the left of each graph. Behavior of other model cells was similar, in that all increased their frequency of oscillation while maintaining similar waveforms and relative phases. Note that the vertical axis gives millivolts relative to the resting membrane potential.

Unfortunately, the oscillatory systems we have identified in this way have not been very robust to small changes in the free parameters. An example of this is given in Fig. 5. This shows the result of increasing one parameter, I_{28}^{tonic}, the amount of depolarizing current injected into cell 28, by only 2%. As can be seen, this change completely alters the system behavior. While not all of the system parameters appear to be this sensitive, many are.

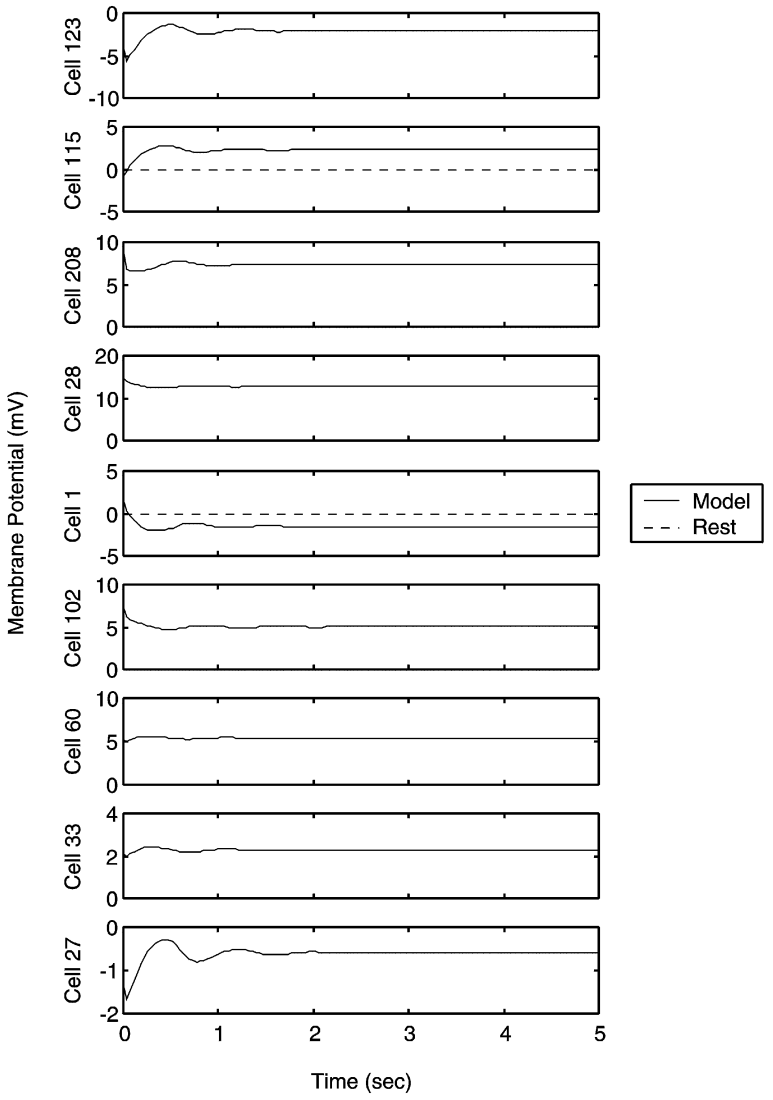

Fig. 5. An example of model behavior when a single parameter, I_{28}^{tonic}, the tonic depolarizing current delivered to model cell 28 for $x(t) = 1$, is increased by 2% from the fit value of 198 pA. The original behavior is shown in Fig. 3. As can be seen, the model no longer oscillates.

7. Discussion

We have shown that a purely passive model is capable of generating an oscillation that is similar to the biological oscillation, and of responding to increasing excitatory input appropriately. However, these models appear to be quite sensitive to small changes in the fit parameters, which is troublesome. Furthermore, the scope of the

testing we have performed on these models in order to compare their behavior to the biological systems' is incomplete. This is an area for future work.

Given the limited testing we have done, it is possible that the sensitivity of our models to small changes in the parameter values is due to the targets being under-constraining for the number of parameters we are trying to fit based on them. If there are many parameter settings giving reasonably good agreement with the targets, then the sensitivity of the models we have found may not be a universal feature of all models fitting the data reasonably well. This needs further investigation, which we are currently undertaking.

Another possibility is that our models are fragile for some more fundamental reason that would hold for any set of parameters fitting the data. One possible reason for fragility is the disparity between the inherent time scale of our model cells and that of the desired oscillation. All of the cells in the model share the same membrane time constant, τ, given by the expression c_m/g_l. In our models, $g_l = 12.5\,\text{nS}$ and $c_m = 0.3\,\text{nF}$, yielding a time constant of 24 ms. This value of τ is probably a reasonable order-of-magnitude estimate based on the available physiological data, which is admittedly rather incomplete. This is compared with the period of the oscillation, which is (typically) 1 s. These differ by a factor of 40, and we believe that this bears directly on the parametric stability of the network. In particular, it can be derived that the relative error in $\dot{v_i}$ (relative to the RMS amplitude), call it ε_v, is approximately given by

$$\varepsilon_v \approx \frac{1}{2\pi} \cdot \frac{T}{\tau} \varepsilon_I \tag{2}$$

where T is the period of the oscillation and ε_I is the relative error in the 'tunable current', i.e. the last two current terms in Eq. (1), which are tunable in that they are changed, for constant v_i, by changing the values of the parameters. Given the values of T and τ, the above expression implies that errors in the tunable current of 5% will give rise to errors in $\dot{v}_i$ of approximately 35%. This is a substantial amplification of error, and may explain why small errors in the system parameters lead to substantial degradation of the behavior. We are in the process of evaluating whether networks of this kind do in fact display increasing sensitivity to parameter noise with increasing T. If this is in fact the case, it would then behoove us to measure the passive time constants of several of the swim CPG cells. If the true values are substantially larger than our estimates, this could explain why our current model is more fragile than we would expect the biology to be.

Our research program has been to begin by trying to understand the leech swim CPG using the simplest possible model, and to turn to more complex models if and when the simpler models were unable to explain the observed behavior. We have not excluded the passive model yet, but if we are unable to adequately model the biology using it, there are a number of possible modifications which are suggested by experiment. One is to add voltage-activated currents to the model cells so that they exhibit the phenomena of post-inhibitory rebound (PIR) and/or membrane relaxation. Both of these phenomena are observed in some cells of the swim CPG, and the

possibility that they could contribute to the generation of the swim oscillation has been suggested [5]. If the passive model should fail, we expect that this, perhaps in concert with other physiologically realistic modifications, will produce systems which more faithfully capture the workings of the biological system.

References

[1] P.D. Brodfuehrer, E.A. Debski, B.A. O'Gara, W.O. Friesen, Neuronal control of leech swimming, J. Neurobiol. 27 (3) (1995) 403–418.
[2] W.O. Friesen, Neuronal control of leech swimming movements: interactions between cell 60 and previously described oscillator neurons, J. Comp. Physiol. A 156 (1985) 231–242.
[3] W.O. Friesen, Neuronal control of leech swimming movements I, inhibitory interactions between motor neurons, J. Comp. Physiol. A 166 (1989) 195–203.
[4] W.O. Friesen, Neuronal control of leech swimming movements II, motor neuron feedback to oscillator cells 115 and 28, J. Comp. Physiol. A 166 (1989) 205–215.
[5] W.O. Friesen, Reciprocal inhibition: a mechanism underlying oscillatory animal movements, Neurosci. Biobehav. Rev. 18 (4) (1994) 547–553.
[6] W.O. Friesen, M. Poon, G.S. Stent, Neuronal control of swimming in the medicinal leech IV, identification of a network of oscillatory interneurones, J. Exp. Biol. 75 (14) (1978) 25–43.
[7] W.O. Friesen, G.S. Stent, Generation of a locomotory rhythm by a neural network with reccurrent cyclic inhibition, Biol. Cybernet. 28 (1) (1977) 27–40.
[8] W.O. Friesen, Neuronal control of leech swimming movements, in: J.W. Jacklet (Ed.), Neuronal and Cellular Oscillators, Marcel Dekker, New York, 1989.
[9] B. Granzow, W.O. Friesen, W.B. Kristan Jr., Physiological and morphological analysis of synaptic transmission between leech motor neurons, J. Neurosci. 5 (8) (1985) 2035–2050.
[10] W.B. Kristan Jr., R.L. Calabrese, Rhythmic swimming activity in neurones of the isolated nerve cord of the leech, J. Exp. Biol. 65 (3) (1976) 643–668.
[11] I. Nabney, Netlab: Algorithms for Pattern Recognition, Forthcoming.
[12] C.A. Ort, W.B. Kristan Jr., G.S. Stent, Neuronal control of swimming in the medicinal leech II, identification and connections of motor neurons, J. Comp. Physiol. 94 (1974) 121–154.
[13] R.A. Pearce, W.O. Friesen, A model for intersegmental coordination in the leech nerve cord, Biol. Cybernet. 58 (5) (1988) 301–311.
[14] B.A. Pearlmutter, Gradient calculations for dynamic recurrent neural networks: a survey, IEEE Trans. Neural Networks 6 (5) (1995) 1212–1228.
[15] J. Weeks, Synaptic basis of swim initiation in the leech II, a pattern-generating neuron (cell 208) which mediates motor effects of swim-initiating neurons, J Comp. Physiol. 148 (1982) 265–279.
[16] J.C. Weeks, Neuronal basis of leech swimming: separation of swim initiation, pattern generation, and intersegmental coordination by selective lesions, J. Neurophysiol. 45 (4) (1981) 698–723.

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Garrison W. Cottrell received his BS in Math and Sociology from Cornell University in 1972, and after years of school bus driving, ice-cream scooping, rough carentry, and auto body work, went back to school and received his PhD from the University of Rochester in Computer Science under James F. Allen in 1985. Following a postdoctoral appointment with David E. Rumelhart in the Institute for Cognitive Science at UCSD, he joined the Computer Science and Engineering Dept. at UCSD, where he is now a Professor. His research interests include cognitive modeling with neural networks, adaptive information retrieval, dynamical systems, computational philosophy, and modeling invertebrate circuits. He is probably best known for his work in image compression and nonlinear dimensionality reduction, word sense disambiguation, and face processing.

William B. Kristan, Jr. received his BA in Biology from Wabash College in Crawfordsville, Indiana in 1964. He completed his Ph.D. work with George Gerstein in the Department of Physiology at the University of Pennsylvania in 1969, using correlations of spike trains to study plasticity in the nervous system of the sea hare. He did two postdoctoral stints, with Donald Kennedy in the Stanford Biology Department, then with Gunther Stent in the Molecular Biology Department at UC Berkeley, in which he honed his skills at tracking down behaviorally relevant neuronal circuits in simple invertebrate nervous systems. He joined the Biology Department at UC San Diego in 1975 and has gleefully watched one of the best neurobiology communities in the world grow up around him. He is now also Director of the Neurosciences Graduate Program. He uses the central nervous system of the medicinal leech to study the neuronal basis of behaviors, behavioral choice, and the development of neuronal circuits. He uses neural models primarily as reality checks in interpreting electrophysiological data.